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TITLE: **Epidemiological Study of Mild Traumatic Brain Injury Sequelae
Caused by Blast Exposure During Operations Iraq Freedom and Enduring
Freedom**

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14. ABSTRACT: Preliminary Results: Accomplishments include initial and ongoing IRB review & approval of all initial submissions, protocol amendments, recruitment advertisements, serious adverse effects, and off-site recruitment activities. We continue to submit to both McGuire and WRAMC IRBs. During Year-3, Camp Lejeune USMC Base was added as a recruitment site. The appropriate US Navy IRB agreed to accept the findings of the WRAMC IRB. All research assistant positions were filled during this reporting period. Study procedures, recruitment, data management, and analyses have been refined through meetings, reviews, consultations, and through lessons learned during completed data collection efforts to date. Subject recruitment and protocol implementation commenced at the VAMC site in 12/08 and at Fort Lee Army Base in 6/09. Through 8/31/11, one hundred sixty one (161) subjects have been accrued (with 152 enrolled) following screen failures) through Polytrauma Network Site Clinic screening, Polytrauma Inpatient Rehabilitation Center, recruitment letters mailed, radio advertisements, posters in the clinics, and on-site enrollment at Fort Lee, VA, USMC Base Camp Lejeune, and USMC Base Quantico. Pending data analysis, most subjects appear to meet symptom criteria for PCS. Conclusions to Date: Enrollment has commenced and continues. Study personnel continue to work with the military partners to improve access to post-deployed service members. The accumulating sample should also be suitable for intervention trials under development. To ensure a sample representative of the target population, we are addressing means to improve access to active duty service members at additional recruitment sites while pursuing expanding outreach to those at existing partner sites.					
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I. INTRODUCTION:

Blast related Traumatic Brain Injury (TBI) is an important source of morbidity in Operations Iraq Freedom and Enduring Freedom (OIF/OEF). Mild TBI (MTBI) may go unrecognized and persist as post-concussion syndrome (PCS). Given that available information is largely anecdotal, the identification, characterization, and prediction of individuals who have PCS with persisting effects from blast-related MTBI are the focus of this series of epidemiological investigations. Multiple hypotheses are being tested including:

- a significant proportion (>18%) of service members experiencing blast events during OIF/OEF sustain a MTBI that leads to persisting symptoms consistent with PCS;
- multiple predictive factors for developing PCS can be identified;
- returnees with PCS will display objective impairments on neuropsychological testing, computerized posturography and/or quantitative electroencephalography; and,
- those with PCS will demonstrate improvement over time but will continue to display significant long-term disability.

A cross-sectional sample of 747 OIF/OEF returnees, who experienced a blast event on tour within the past two years, will undergo three phases of evaluations as follows:

- Phase-I: will determine the sample prevalence of PCS after blast related MTBI, characterize the constellation of related symptoms and problems, and allow predictive modeling.
- Phase-II: will utilize a case-control design to evaluate objective abnormalities among the subjects with PCS after MTBI.
- Phase-III is a longitudinal design using repeated measures for analysis of outcomes over time (baseline, 6 months, and one year).

II. BODY OF REPORT: Accomplishments relative to our Statement-of-Work (SOW):

A. SOW Task 1 - Objective: prepare and initiate the overarching research study plan.

1. Obtain IRB approval for project [Ms. Nichols]:

Approval from the primary institutional review board, the McGuire IRB was obtained on August 15, 2008. Secondary IRB approval from USAMRMC (Fort Detrick IRB) was received on September 27, 2008. Virginia Commonwealth University IRB approval was received on March 5, 2009.

All amendments, updated staff rosters, SAEs, and continuing reviews have been submitted to primary and secondary IRBs as required.

2. Establish Military site screening/recruitment options [Ms. Nichols & Dr. Walker]:

Full Walter Reed AMC IRB approval, as required by the Fort Lee base commander, was received on June 10, 2009 after extensive planning and preparation. The CDMRP research team began the recruitment and screening process at Kenner Army Health Clinic at Fort Lee on 6/19/2009. Kenner site recruitment is ongoing.

Contacts and processes were established to add an additional military recruitment site at US Marine Corps Base (MCB), Quantico, Virginia, and a Letter of Collaboration and Support was sent to the Command at MCB Quantico. Ms. Nichols worked with the Department of Navy Human Research Protection Program (DON HRPP) to address the regulatory and logistical requirements of adding Quantico as a recruitment site. DON HRPP determined that an additional Navy IRB review would not be necessary (as protocol has already been reviewed/approved by the following: McGuire IRB, VCU IRB, WRAMC IRB and USAMRMC). The McGuire VAMC and McGuire Research Institute added an FWA addendum as requested by DON HRPP. The lengthy regulatory and logistic requirements were completed and recruitment at the Quantico site commenced on June 9, 2010. The above avenues have not met our expectations regarding volume of eligible active duty subjects, so efforts on this objective continue. Communications and planning are ongoing to expand recruitment efforts on Quantico MCB beyond the PDHRA clinic and directly to approved military commands. The addition of a third external recruitment site was deemed necessary and steps were taken to add MCB Camp Lejeune as a site. All necessary letters of support and regulatory approvals, following a subsequent amendment to the original protocol, were obtained. Recruitment at MCB Camp Lejeune commenced in April 2011 and is ongoing. Unfortunately while there appears to be a large number of eligible individuals at Lejeune, military command and control restraints have limited our access for screening and evaluating subjects. We are now working on IRB approvals to administer phase 2 evaluations on-site at Lejeune to minimize disruptions to the military structure.

3. Establish availability and content of acute injury (war-zone) variables. [Dr. Walker]

After determining that acute injury documentation was not reliably available post-acutely, we refined our injury situation and experience questionnaires to be as thorough and specific as possible. Additionally, we chose to add two structured interviews to help cross-validate some of our key diagnostic screening questionnaires. These processes were completed last reporting year.

4. Finalize Data collection forms including TELEforms. [Ms. Nichols, Drs. McKinney, Cifu, & Walker]

Completed during Year One for initial study approval. Changes to data collection instruments, including TELEforms have been made to remain consistent with protocol amendments and our data auditing findings and conclusions. All form revisions were submitted for respective IRB approvals, as part of the amendment submission packets.

5. Complete set-up of data management software system. [Mr. Bush]

Accomplished.

6. Establish logistics (when, where, workspace) for study screening and recruitment of military personnel at Central Virginia PDHA clinic sites. [Dr. Cifu & Ms Nichols]

Thus far, the volume of eligible subjects identified at Kenner Army Health PDHRA clinics has been far below anticipated. Therefore we have continued to explore and pursue recruitment opportunities outside of the PDHRA clinics. We continue to work on this effort. At Fort Lee we have sent staff to all large group briefings and the PDHRA clinic one to three times per week. We have been notified that effective September 2011, our POC will be moved to another area and we will no longer have the same level of access. We have created a pamphlet to leave on site with the clinic personnel and in the waiting rooms. Once a Registered Nurse is hired for the clinic, Dr. Walker and Ms. Nichols will schedule a meeting to address recruitment needs on base. We continue to have the support of the Fort Lee Site PI. At MCB Quantico, Ms. Nichols continues to collaborate with the Wounded Warrior Regiment and Command to facilitate access to Marines and both Dr. Walker and Ms. Nichols have been collaborating with the Command at MCB Camp Lejeune to facilitate access to additional battalions. We continue to screen all patients seen within the Polytrauma program at the McGuire VAMC and send recruitment letters to all individuals who have registered as having served in OEF/OIF conflicts.

7. Hire and train study coordinator and other TBH study personnel. [Hiring: Mr. Heimiller, Training: Ms. Nichols & Drs. Nelson & McDonald]:

Please see the table below for study staff name, role, and effort. Mr. Heimiller and Ms. Nichols helped write/prepare the original application, and have been continually involved in this project from its inception. Dr. McDonald, research psychologist joined us in August, 2008, and continues to contribute to various aspects of the project. After award and funding were received, the above individuals continued in part-time paid roles. Ms. Emily Lynn and Ms. Jasmine Smith, both full time research assistants, were hired during the previous reporting period. Lonnie A. Nelson, PhD., Research Psychologist, Fort Carson DVBIC, Fort Carson, Colorado, is an expert in the field of qEEG applications and analysis. Dr. Nelson is assisting with interpretation and analysis of qEEG testing. Mr. Peter Temple and Ms. Nichole Kelly were added to the study personnel team as research assistants in 2010 (in non-compensated roles). Both Mr. Temple and Ms. Kelly are graduate students and left the program at the end of the 2011 academic year.

Recent changes to the VCU Subaward include: Mr. Brian Bush effort reduction from 50% to 5%; and, Ms. Huan Wang added to project as data analyst (20% effort).

CDMRP/Walker: Study Staff (Compensated) Summary

NAME & ROLE	MONTH/YEAR HIRED	% EFFORT
William C. Walker, MD, Principal Investigator	September, 2008	20 (see: VCU sub-award)
David X. Cifu, MD Co-Investigator	September, 2008	5 (VCU sub-award)

Jessica McKinney-Ketchum, Ph.D, Biostatistics	September, 2008	10 (VCU sub-award)
Brian J. Bush, MSMT Data Manager	June, 2009	5 (VCU sub-award)
Huan Wang Data Analyst	Subaward: Year-3	20 (VCU sub-award)
Michelle Nichols, MSN, RN, Co-Investigator & Clinical Research Coordinator	September, 2008	20
Jerome Heimiller, RPH, MPA, Administrator	September, 2008	(up to) 10
Tiffany Clory, BS, Research Assistant	November, 2008 (<i>Departed Program: July, 2010</i>)	100
April Dean, BS, Research Assistant	January, 2009	100
Tammy Searles, RN, Lead Research Assistant	June, 2009 (<i>Departed Program: Jan., 2009</i>)	100
Scott McDonald, PhD., Research Psychologist	September, 2008	(up to) 10
Emily Lynn, BA Research Assistant	April, 2010	100
Jasmine Smith, BA Research Assistant	June, 2010 (<i>Departing Program: 9/23/2011</i>)	100

B. SOW Task 2 - Objective: Determine the prevalence of PCS after blast related MTBI in OIF/OEF to better define the scope of residual injury and determine early factors predictive of PCS after blast injury to aid the development of better secondary prevention and treatment strategies. Timeline for all subtasks: Gradually accrue over 4 years 747 subjects total (50 subjects by end Year 1, 325 subjects by end Year 2, 600 subjects by end Year 3, 747 subjects by end Year 4) into Phase-I. Responsible personnel: listed below for each subtask [].

1. Consent & Enroll 747 Subjects Total. [Ms. Nichols, Dr. Walker, Research Assistants]

Through August, 2011, two thousand seven hundred fifteen (2,715) potential subjects have been screened, and one hundred fifty-two (152) subjects have been enrolled. Please see “Appendix #1” for a demographic breakdown of enrolled subjects. Enrollment started slowly due to the lag time between selection and meeting USAMRAA pre-funding requirements, and the period devoted to recruiting/appointing our three full-time study staff. As noted previously, the requirement for an additional army IRB review delayed enrollment at Kenner Health Clinic. We found that many of the patients screened at VAMC Polytrauma

Network Clinic who screened positive for blast exposure during OIF/OEF deployment were not eligible because the exposure was more than 2 years prior. We expanded our Richmond (McGuire) VAMC recruitment through outreach letters to registered patients and created a poster (see APPENDIX # 2) to be displayed to enhance subject recruitment efforts. Through August 31, 2011, we have mailed out 9,303 recruitment letters to subjects/patients who were registered at the Richmond VA Medical Center, and had served in OIF or OEF. And as noted previously, we also opted to pursue an additional military recruitment site (Quantico, Virginia US MCB). Neither of the added military sites has yielded the anticipated volume of eligible subjects, so we are continuing to pursue additional recruitment opportunities (besides PDHRA clinics) at Fort Lee and Quantico. We also completed the necessary approvals for advertisement and recruitment at Camp Lejeune Marine Base, NC which has begun as previously noted. Previously approved advertisement (flyer) has been fully implemented in recruitment efforts in the Central Virginia area and a radio advertisement was created, received full IRB approval, was implemented and subsequently discontinued due to insufficient response to justify continued expense. The intended goal of the radio advertisement had been to extend an invitation for screening and potential participation to a larger geographic catchment area of individuals who are post-deployed OEF/OIF Service Members or Veterans yet are not currently followed in any of the existing clinical environments we are recruiting from. The radio advertisement unfortunately yielded only one subject.

2. For each subject above, complete standardized current state questionnaires for qualitative and quantitative measurement of: Post-concussion syndrome (PCS) using the Rivermead Post-Concussion Symptoms Checklist (RPQ) (King, 1995), Combat Stress using the PTSD Checklist Military Version (PCL-M) (Weathers et al, 1991), pain using both the McGill Pain Questionnaire short form (MPQ-SF) (Melzak, 1987) and the 11 point Numerical Scale (Jensen MP et al, 1989), and affective disorder using the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The ICD-10 criteria for PCS will be used to categorize the cases with PCS for the prevalence numerator, subjects with PCS after OIF/OEF blast exposure Injury (Boake, 2005; WHO, 1992; WHO, 1993). The International Classification of Diseases is published by the World Health Organization (WHO). The ICD-10 criteria for PCS are 1) a history of MTBI and 2) a minimum of 3 of following symptoms (present to a moderate degree compared to pre-morbid): headache, dizziness, fatigue, irritability, insomnia, poor concentration, memory problems, or intolerance of stress, emotion, or alcohol. The RPQ is being utilized to standardize this diagnostic assessment. [Oversight: Ms. Nichols, Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on the 152 subjects enrolled through August 31, 2011.

3. For each subject, collect blast injury and individual characteristics data including: dazed, memory gap (injury, pre-injury, and post-injury), lost consciousness, stress, pain, helmet wearing, shrapnel injury, tympanic membrane rupture, hearing loss, type of blast, immediate blast effects, number of blast exposures, demographic, education level, psychiatric history, medical history, and time since injury. These variables will be collected using a series of questionnaires including: Full Blast Questionnaire (modified version of Walter Reed Blast Inventory (Scherer et al, 2007), see Protocol), a Health History Questionnaire (see Protocol), the recalled immediate psychological stress of the blast event using the Impact of Events Scale (IES) (Horowitz et al, 1979), the recalled physical pain level of the blast event using the 11 point Numerical Scale

and the Alcohol Use Disorders Test-Consumption (AUDIT-C), a brief screening tool for heavy drinking and/or active alcohol abuse/dependency (Bradley et.al., 2007). [Oversight: Ms. Nichols, Dr Walker and Dr Cifu. Scheduling: Research Assistants. Monitoring and facilitation of subject form completion: Research Assistants]

Accomplished on the 152 subjects enrolled through August 31, 2011.

4. For each subject, the study biostatistician will designate a group assignment (with PCS versus without PCS) using a predetermined threshold of MTBI symptom severity (ICD-10 diagnostic criteria applied to the RPQ data) in order to derive prevalence of PCS and to select subjects for Task 3 [Dr. McKinney]

Accomplished on the 152 subjects enrolled through August 31, 2011.

5. Study biostatistician will provide interval (monthly) updates of the ratio of PCS to no PCS group membership to the PI for the purpose of monitoring accrual targets and trends, but will otherwise will not reveal assignment to either subject or study staff (double blind). [Dr Ketchum]

Accomplished on the 152 subjects enrolled through August 31, 2011.

6. Perform data audits after first subject completed Phase 1 and on 5% of accrual target (37 subjects) on a monthly basis. [Dr. McKinney]

During the first year cycle, data auditing occurred on the first subject and has continued to date. In May 2009, on April 15, 2010, and again in May 2011, this study was audited by the VA Research Compliance Officer, as part of their Standard Operating Procedures and it was found at that time to be 100% compliant. Phase I, II and III data audits have been performed on study visits through August 2011 and as such have exceeded the target of auditing 5% of accruals. This process has been maintained while accrual rates are lower and has ensured data integrity and accuracy of new personnel in addition to inter-rater reliability. As accruals increase toward targeted goals, a minimum of 5% of all accruals will be audited on a monthly basis.

7. Using a case-control design (PCS versus no PCS) and adjusting for PTSD, several statistical analyses will be performed including two-way analysis of variance (ANOVA) (to compare quantitative variables), chi-square tests (to compare proportions of qualitative variables, and a multiple logistic regression model (to determine the predictive nature of these variables as a group). PTSD will be measured as a continuous variable using the PTSD Checklist – Military Version (PCL-M) total score. These analyses will determine factors associated with (or predictive of) developing PCS after blast related MTBI. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

Pending complete enrollment and data collection.

C. Task 3 - Objective: Identify and describe objective cognitive performance and neuro-physical impairments in returnees with PCS after blast-related MTBI incurred during OIF/OEF (Study Phase 2). Timeline: Gradual accrual into Phase 2 of minimum of 284 total subjects over 4 years (30 subjects by end Year 1, 125 subjects by end Year 2, 225 subjects by end Year 3, 284 subjects by end Year 4). Responsible personnel: listed below for each subtask [].

1. At least monthly, groups of subjects who completed Phase-I (Task 2 above), will be assigned to enter Phase-II evaluations as follows: With PCS (all), Without PCS (equal number to "With PCS" who are selected using described randomization scheme). [Ms. Nichols & Dr. Walker]

Accomplished on the 152 subjects enrolled through August 31, 2011.

2. Study biostatistician will provide the study coordinator with a list (at least monthly) of de-identified subjects who are assigned for Phase-I evaluations, but will NOT reveal group assignment (With PCS versus Without PCS) to study staff or subject (i.e. to minimize bias of objective evaluations during Phase 2, double blinding of group assignment will be maintained). [Dr. Ketchum]

Accomplished on the 152 subjects enrolled through August 31, 2011.

3. For each Phase-II subject, conduct objective evaluations and collect data including full neuropsychological batteries (cognitive performance and fine motor assessment), quantitative electroencephalography (neurophysiologic cognitive assessment), and computerized posturography (balance impairment assessment). CPT will consist of The Sensory Organization Test (SOT), a composite index that defines abnormalities across somatosensory, visual, and vestibular systems. QEEG recordings will consist of baseline 10 minute eyes closed and a 10 minute eyes open resting period. There are multiple normative databases for comparison of individual electrocortical activity. The "life-span" database included with the Neuroguide® EEG analysis software consists of 625 records from normal individuals ranging in age from 2 months to 89 years. Neuroguide® also includes a discriminant function analysis to calculate the probability that a person has sustained a TBI based on their eyes closed resting baseline recording alone. In the initial validation study, a sensitivity of 95.45% and a specificity of 97.44% were reported for classification accuracy in comparison to normals. This discriminant function was developed based on the work of Thatcher and others with the Defense and Veterans Head Injury Program (DVHIP) in the 1990's and used a sample of veterans from what have become the lead Polytrauma centers within the Veterans Affairs health care system (Palo Alto, CA, Minneapolis, MN, Richmond, VA, and Tampa, FL). Thus, it is an appropriate comparison group for our purposes. The neuropsychological battery will consist of the following standardized, validated, tests of proven reliability: Wechsler Test of Adult Reading (WTAR, pre-morbid IQ estimate),(Mathias, Bowden, Bigler, & Rosenfeld, 2007) Conners Continuous Performance Test-II (CCPT-II, sustained attention),(Conners, 2000) Paced Auditory Serial Addition Test (PASAT, processing speed),(Vanderploeg, Curtiss, & Belanger, 2005) Halsted-Reitan Trail Making Test A & B (TMT, visual scanning and executive function),(Lange, Iverson, Zakrzewski, Ethel-King, & Franzen, 2005) Stroop classic test (target processing speed and divided attention),(Soeda et al., 2005) Grooved Pegboard to asses fine motor speed and dexterity (Hanna-Pladdy, Mendoza, Apostolos, & Heilman, 2002), Test of Memory Malingering (TOMM) (Tombaugh, 1997) California Verbal Learning Test-II (CVLT-II) (learning and working memory),(Vanderploeg et al., 2005) Wechsler Adult Intelligence Scale III (WAIS-III) items: Digit Symbol Coding, Digit Span, Letter-Number Sequencing, Symbol Search, & Arithmetic (processing speed, attention, and working memory),(McKay, Casey, Wertheimer, & Fichtenberg, 2007) Delis-Kaplan Executive Function System (D-KEFS) Category Fluency (Animals And Boys' Names) (Harrison, Buxton, Husain, & Wise, 2000):Controlled Oral Word Association Test single letter and

category items (COWAT, verbal fluency), (Iverson, Franzen, & Lovell, 1999) Benton Visual Memory Test-Revised (BVM-T-R) (visual perception and memory). (Morey, Cilo, Berry, & Cusick, 2003) [Test scheduling: M. Nichols, MSN, RN and Research Assistants; Neuropsychological testing: Trained Research Assistants, Ms. Nichols, & Dr. McDonald. QEEG testing: Ms. Nichols, MSN, RN, and trained research assistants.]

Accomplished on the 115 subjects who have completed Phase-II.

4. Use this data to perform and fit several two-way ANOVA models with main effects for PCS (present/absent) and cognitive or neurological impairment (present/absent). A separate model will be fit for each response variable. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

Pending complete enrollment and data collection.

5. Determine the sensitivity and specificity for detecting neurophysiologic abnormalities after MTBI from blast injury during OIF/OEF using QEEG with the goal of assessing the accuracy of detection of mild TBI using a purely neuro-physical method of measurement. [Statistics: Dr. Ketchum. Interpretation: all key investigators]

Pending complete enrollment and data collection.

6. Determine the feasibility of a functional magnetic resonance and diffusion tensor imaging pilot descriptive study (anatomic/physiologic assessment) in a subset of cases and controls. [Dr. Walker, Ms. Nichols]

Dr. Walker and Ms. Nichols continue to meet with Richmond VAMC radiology staff and other key personnel to establish a pilot DTI protocol. The protocol "*Diffusion Tensor Imaging and Post-Concussion Syndrome: A Feasibility Study*" (PI: Walker) was written and received IRB approval on 4/24/2009. The RVAMC purchased a 3.0 Tesla MRI scanner that will be used in this study. Due to ongoing radiology technician shortages at the RVAMC, progress has stalled on the Diffusion Tensor Imaging feasibility project as an additional Phase-II measure for a subset of subjects. Discussions took place with radiology investigators at John Hopkins University regarding transporting the subjects up there to obtain the study on their state-of-the-art Telsa-7 scanner. This feasibility protocol remains "pending".

D. Task 4 - Objective: Assess the sensitivity and specificity within this sample of select key diagnostic questionnaires used in Phase 1 relative to "gold standard" structured interviews.

1. Structured interviews will be added to Phase-II measures for: Major Mental Health disorders (Major Depressive Disorder, Bipolar Disorder, Panic Disorder w/ w/o Agoraphobia Social Anxiety Disorder, Specific Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder, and Psychotic Disorders) using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998); PTSD using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995); mild blast related TBI using an instrument newly developed for this study loosely based on existing interviews used in acute rehabilitation settings (e.g., Gioia et al., 2008). [M. Nichols, MSN, RN, Dr. McDonald, Dr. Cifu, Dr. Ketchum, and Dr. Walker]

Accomplished last reporting year. Interviewer auditing and as needed training continues.

2. Collect these interview measures in the subsequent approximately 200 subjects entering Phase 2. [Ms. Nichols, Dr. McDonald, Dr. Walker, Trained Research Assistants]

Phase-II activity (see D1 above). Commenced in Year Two and was completed on 14 subjects through August 2010 (end of Year-2). Through August, 2011 (end of Year-3); structured interviews have been completed on 67 subjects.

3. Analyze findings and implications for the primary analyses described in Tasks 2 and 3. [Dr. Ketchum, Dr Walker, and all investigators]

Phase-II analytical activity (see D1 above). Not applicable to current progress report.

- E. **Task 5: Determine the trajectory of symptoms and social/vocational functioning in PCS after blast related MTBI (Study Phase-III). Timeline: Gradual accrual into Phase 2 of 225 total subjects over 4 years (25 subjects by end Year 1, 125 subjects by end Year 2, 2225 subjects by end Year 3). Responsible personnel: listed below for each subtask [].**

1. On over 232 returnees (consecutive Phase-I enrollments described in Task 1 & 2), collect follow-up longitudinal data (6 months, and one year) on phase-I current-state measures, AND collect complete longitudinal outcome data (6 months and one year) using standardized and validated TBI specific outcome measures including: Extended Glasgow Outcome Scale (GOS-E) (Wilson et al, 1998) (global outcome), Mayo-Portland Adaptability Inventory-4 (MPAI-4)(Malec, 2004) (ability, participation, adjustment), and the Satisfaction With Life Scale (SWLS) (Diener et al, 1985) (quality of life). [scheduling: Ms Nichols. Telephonic or in-person data collection: Research Assistants]

Completed Phase-III (6 month) evaluations, on 76 subjects through August 31, 2011.

Completed Phase-III (12 month) evaluations, on fifty-four (54) subjects through August 31, 2011. Completion of Phase-III evaluations has been hindered by subject relocation and or redeployment and is below our expectations. Thus, we have instituted additional strategies to optimize our Phase-III retention rate. These additional strategies have facilitated improvement of the collection of final outcome data. We continue to monitor progress on this and track those participants who are deployed at the time of study visits.

2. Describe the trajectory of symptoms and social/vocational functioning among returnees with PCS after blast-related MTBI. [Analysis by all key investigators]

Pending complete enrollment and data collection.

3. Conduct statistical analysis using repeated measures mixed-models for analysis of outcomes over time (baseline, 6 months, and one year). [Statistics: Dr Ketchum, Interpretation: All key investigators]

Pending complete enrollment and data collection.

F. Task 6 – Objective: Disseminate Findings:

1. Disseminate results via publication in peer reviewed journals. [All key investigators coordinated/led by Dr. Walker]

Walker, W., Nichols, M., McDonald, S., Ketchum, J., & Cifu, D. (Under review). The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome. Submitted to *Journal of Head Trauma Rehabilitation*.

2. Present at professional meetings to reach the variety of practitioners treating TBI and blast injured patients [All key investigators coordinated/led by Dr. Walker].

Kelly, N.R., McDonald, S., Ketchum, J.M., Nichols, M., & Walker, W. (2011, June 13-15). Balance and cognitive functioning: Associations following blast exposure. Poster presented at the 3rd Federal TBI Interagency Conference in Washington, D.C.

Walker, W., Nichols, M., McDonald, S., Ketchum, J., & Cifu, D. (2011, November 17-20). The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome. Accepted for presentation as a poster at the 2011 AAPM&R Annual Assembly in Orlando, Florida. Poster was selected as part of Best Neuroscience Research Presentation.

III. KEY RESEARCH ACCOMPLISHMENTS:

- Developed structured interview for the post-acute detection/diagnosis of mild TBI. Such an instrument did not previously exist in the published literature.
- Additional “key” research accomplishments are expected in year four. For year three accomplishments, please see “II” above (pages 4-12).

IV. REPORTABLE OUTCOMES:

Award Years One & Two

- Oral Symposium presentation, Military Health Research Forum, Kansas City, MI, Sept 1, 2009 (previously submitted)
- Poster presentation, Military Health Research Forum, Kansas City, MI, Sept 2, 2009 (previously submitted).

For Award Year Three:

POSTER PRESENTATIONS:

Presented:

- Kelly, N. R., McDonald, S., Ketchum, J., Nichols, M., Walker, WC.. Balance and Cognitive Functioning: Associations Following Blast Exposure. Federal Interagency Conference on Traumatic Brain Injury, Washington, DC, June 13-15, 2011(see attachment # 2).

Accepted and Selected for Neurologic Best Research Presentations:

- Walker WC, Nichols M, McDonald S, Cifu DX. The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome. Amer Academy Phys Med Rehabil Annual Assembly, November 2011, Orlando, FL. (see attachment #: 3 poster abstract)

V. CONCLUSION:

When completed, this study, by identifying factors that predispose service-members to PCS after blast-related MTBI, will aid in developing targeted secondary prevention strategies. Characterization of the impairments and problems related to PCS will aid health care planning and developing targeted medical and rehabilitative treatment strategies.

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VII. APPENDICES:

APPENDIX # 1: ***Subject Demographics through Year-III***

CDMRP Demographic Summary Sheet: Updated September 20, 2011 (N = 144 Subjects)

Variable	Mean	SD	Range
Age	28.13	7.84	19 – 60
	Count	Percent	
Sex			
Male	139	96.5	
Female	5	3.5	
Marital Status			
Married	64	44.4	
Divorced	14	9.7	
Single	66	45.8	
Race			
Caucasian	109	76.2	
African American	23	16.1	
Other ¹	11	7.7	
Ethnicity			
Hispanic	16	11.3	
Non-Hispanic	125	88.7	
Highest Level of Education			
High School Graduate	71	49.3	
Some College	55	38.2	
College Graduate	17	11.8	
Post-Graduate Degree	1	0.7	
Prior Deployment Status			
Active Duty	103	71.5	
Selective Reserves – National Guard	25	17.4	
Selective Reserves – Reserve	10	6.9	
Ready Reserves	4	2.8	
Civilian Government Employee	1	0.7	
Other (Contractor)	1	0.7	

¹ Other Race includes: 1 Black/White, 6 Hispanic/Latino, 1 Native American, 1 Native American/Black, 1 White/Asian, and 1 unknown (missing).

Balance and Cognitive Functioning: Associations Following Blast Exposure



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INTRODUCTION

- Balance and cognitive functioning are significant contributors to functional outcomes and independent living among individuals with traumatic brain injury (Catena et al., 2007; McCulloch et al., 2010).
- Associations between these variables has been observed in healthy and cognitively impaired older adults (Haggard et al., 2000; Holtzer et al., 2007), as well as adults with head injury (Basford et al., 2003; Sosnoff et al., 2008; Vanderploeg et al., 2005, 2007).
- Whereas recent studies have drawn attention to the sequelae of blast injury, the relation between balance and cognitive functioning has yet to be explored in blast-exposed individuals.

METHODS

Participants:

- Eligibility criteria for larger epidemiological study:**
 - Military or Veteran Healthcare Beneficiaries
 - Post Deployment status after having served in OIF and/or OEF
 - Exposed to blast during deployment within past 2 years
 - Excluded if had severe TBI or had TBI of primary etiology other than blast
- Additional criteria for current study:**
 - Epidemiologic study Phase 2 evaluations completed* (n=57)
 - Valid balance testing (one outlier excluded)
 - Valid Phase 2 testing effort (two excluded using TOMM criteria)

*neuropsychological data was not available on one subject, thus testing data is reported on final n=53

Participant Demographic Information:

- N = 54; 90.7% male; median age = 27 (range 20 – 57 years)
- 67% Caucasian, 28% African American, 6% Other
- 48% Active Duty, 37% National Guard / Reserves
- Median months since blast = 14.3 (range 1.4 – 66.0)*

*for those with multiple blast exposures, value is time since most recent of blast two to three years

Cognitive Measures:

- Conners' Continuous Performance Test-II (CPT-II)
- California Verbal Learning Test-II (CVLT-II)
- Wechsler Test of Adult Reading (WTAR)
- Wechsler Adult Intelligence Scale III (WAIS-III):
 - Digit Symbol Coding (DSC), Letter-Number Sequencing (LNS), and Symbol Search (SS)
- Delis-Kaplan Executive Function System (DKEFS):
 - Verbal Fluency, Category Fluency, and Category Switching
- Test of Memory Malingering (TOMM)
- Benton Visual Memory Test-Revised (BVMTR)

Balance:

- Postural stability was assessed using a dual-phase force platform, the NeuroCom Smart Balance Master (NeuroCom International, Inc, Clackamas, OR). The composite equilibrium score from The Sensory Organization Test, used here, is an index of overall balance performance

Based on standardized balance scores, participants were classified as having below ($Z \leq -1$) or above average ($Z > -1$) balance.

Statistical Procedures

- Correlation analyses between standardized balance scores and cognitive measures were conducted overall for all 54 participants.
- Independent samples t-tests were conducted to evaluate cognitive performance between those with above and below average balance scores.

Results

- 12 participants (22%) had below average balance performance ($Z < -1$ on Sensory Organization Test)
- Significant positive correlations were found between balance and measures of executive functioning (all DKEFS measures), processing speed (SS), working memory (LNS) and nonverbal delayed recall (BVMTR-Delayed Recall). There was also a significant negative relationship between balance and behavioral inhibition (CPT-II Commissions). Refer to Table 1.
- Independent-samples t-tests indicated that participants with below average balance scored lower on measures of executive functioning (DKEFS Verbal and Category Fluency), processing speed, and working memory. Refer to Table 2.
- Performance on verbal fluency and working memory was in the Low Average range for those with below average balance in contrast to the Average range for those with above average balance.
- The below average balance group also scored lower on measures of cognitive flexibility (DKEFS Category Switching), nonverbal delayed recall, and attention, although differences were not significant.

Conclusions

- Despite not sustaining severe TBI, balance performance was below average in approximately one quarter of this sample evaluated at a median of 14.3 months after last military-related blast exposure. Balance performance was negatively associated with several indicators of executive functioning (i.e., verbal fluency, cognitive flexibility, and response inhibition), as well as processing speed and working memory.
- Proposed explanations among other clinical samples for concurrent impairments in cognition and balance include: common neurological pathways, limited attentional capacity and/or difficulties allocating attention to both tasks (i.e., executive dysfunction), and mood-related neurochemical activities (e.g., Brenner et al., 2010; McCulloch, 2007).
- Outcomes from this study support the contention that shared neurobiological underpinnings, perhaps frontal lobe systems, are responsible for observed simultaneous impairments in cognition and balance among blast-exposed individuals.
- Although replication is needed with larger, more diverse samples, the current study's findings are quite robust in light of the sample size and thus have implications for rehabilitation efforts with blast-exposed individuals (e.g., targeting single rather than multiple systems, modifying communication patterns during single- and dual-task conditions).
- Future research should explore the potential moderating or mediating role of a number of third variables (e.g., mood, sleep, pain) on the association between balance, blast-exposure, and cognitive functioning.

Table 1. Correlations

	Balance	Processing Speed	Working Memory	Verbal Fluency	Category Fluency	Category Switching	Nonverbal Delayed Recall	Behavioral Inhibition
Balance	1.00							
Processing Speed	0.32*	1.00						
Working Memory	0.38*	0.45*	1.00					
Verbal Fluency	0.35*	0.28	0.32*	1.00				
Category Fluency	0.31*	0.25	0.30*	0.42*	1.00			
Category Switching	0.29	0.22	0.28	0.38*	0.35*	1.00		
Nonverbal Delayed Recall	0.33*	0.27	0.31*	0.36*	0.33*	0.41*	1.00	
Behavioral Inhibition	-0.28	-0.21	-0.25	-0.22	-0.20	-0.23	-0.21	1.00



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Table 2. Independent Samples T-Tests

	Below Average Balance	Above Average Balance	t	df	p
Processing Speed	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Working Memory	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Verbal Fluency	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Category Fluency	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Category Switching	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Nonverbal Delayed Recall	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04
Behavioral Inhibition	10.5 (SD=1.2)	11.5 (SD=1.1)	-2.1	52	.04

NOTES: *p < .05. We would like to thank the many research and active duty military personnel who kindly volunteered for this research for both their participation and service to our country. We would also like to thank Jordan Stangor, Angela Stangor, and April Chen for their diligence and assistance in making this project possible. Views expressed in this presentation are those of the authors and do not necessarily represent the views of DOD, the Department of Defense, or other author affiliations. Please address correspondence about this work to: William C. Walker, MD, DABCC, Research Services (111) (121) Broad Bush Road, Richmond, VA 23244 or Walker.Peter@va.gov.

Appendix # 3

Title: The identification of transient altered consciousness induced by military related blast exposure and it's relation to post-concussion syndrome.

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ABSTRACT:

Objective: To analyze the inter-item agreement and relationship to current symptoms of questionnaire responses for recalled symptoms of altered consciousness in subjects who may have sustained a blast associated mild Traumatic Brain Injury (TBI) in the past two years.

Design: Prospective cohort study.

Setting: Outpatient Clinics at a Veterans Affairs Polytrauma Rehabilitation Center and participating Military Treatment Facilities.

Participants: Eighty-nine active duty or Veteran subjects who experienced acute effects from a blast within the past 2 years while deployed in support of Operations Enduring and Iraqi Freedom; Severe TBI was an exclusion criterion.

Interventions: Not applicable.

Main Outcome Measures: Standardized, self-report measures of current post-concussive symptoms (PCS) using the Rivermead Post-Concussion Symptom Questionnaire (RPQ), Posttraumatic Stress Disorder (PTSD) using the PTSD Checklist, Civilian Version (PCL-C), depression using the Centers for Epidemiological Studies Depression Scale (CES-D), and pain using the Short Form McGill Pain Questionnaire (SF-MPQ).

Results: Thirty-one subjects (34.8%) responded positively to at least one of three

concrete altered consciousness items: gap in memory (19.1%), memory not continuous (15.7%), and/or told by observer they had loss of consciousness (LOC; 21.3%). There was evidence of significant agreement between memory gap and memory not continuous (87.6% concordant; kappa = 0.57, 95% CI = 0.35, 0.80). As expected, since LOC is not necessary when there is amnesia, concordance was lower between LOC and memory not continuous (80.9% concordant), and between LOC and memory gap (77.5% concordant). Each altered consciousness item was predictive of current symptom distress.

Conclusion: All altered consciousness questionnaire responses suggesting TBI were predictive of current symptom distress in this population. Some inconsistencies were found in subjects' item responses, suggesting structured interview may improve diagnostic accuracy for TBI.

Key Words: Brain Concussion, Military Medicine, Post-concussion Syndrome, Questionnaire

VIII. SUPPORTING DATA: Please see table and figures above. No additional supporting data at this time (Year-III).